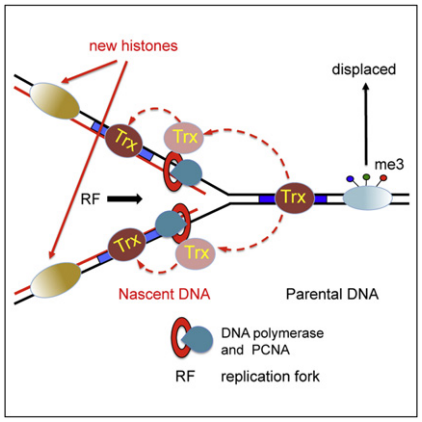
In This Issue

Cell



Still Standing in the Replisome's Wake

PAGE 922

What survives the replication fork during DNA synthesis and cell division to make a so-called epigenetic mark truly heritable? Looking at the molecular level, Petruk et al. now provide evidence using ChIP and re-ChIP experiments, as well as a newly developed chromatin assembly assay, that Trithorax and Polycomb complexes, rather than modified histones, could provide persistent marks on DNA following replisome passage.

No Passenger, No Problem for RNAi

PAGE 883 and PAGE 895

Classical RNAi approaches rely on loading double-stranded RNAs into the RISC complex. Two papers in this issue show that single-stranded RNAs can be efficacious in RISC complexes as well. Lima et al. develop single-stranded RNAs containing chemically modified nucleotides and a 5'-phosphate analog for RNAi-based applications via Ago2-based cleavage in mice. Using similarly modified RNA oligonucleotides, Yu et al. demonstrate allele-selective targeting of mutant huntingtin throughout the brain in a mouse model of Huntington's disease. In this setting, the choice of the RNA sequence drives a miRNA-like mechanism of action. These papers open up the prospect of using stabilized single-stranded RNAs in therapeutic applications based on RNAi pathways.

Polymerase Stops on a J

PAGE 909

Trypanosomes and *Leishmania* are human parasites that harbor a modified DNA base, β-D-glucosyl-hydroxymethyluracil, often called base J. Van Luenen et al. now show that base J is present at RNA Pol II transcription termination sites, and if the base is removed, the polymerase fails to stop, resulting in massive transcriptional readthrough and death of the parasite. The findings indicate a new mode of transcriptional termination.

Histone Methylation Quiets Chromatin at the Periphery

PAGE 934 and PAGE 948

Heterochromatin and euchromatin are often segregated in eurkaryotic nuclei, but the factors that drive this organization are not fully understood. Two papers now show that, in both nematodes and mice, trimethylation of lysine 9 on histone H3 (H3K9) drives heterochromatin anchoring to the nuclear envelope and ensures transcriptional repression at heterochromatic sites. However, different enzymes initiate H3K9 methylation in nematodes and mice. Towbin et al. show that, in *C. elegans*, MET-2 deposits the first two methyl groups and SET-25 (a Suv39h enzyme) the third. In mice, Pinheiro et al. show that Prdm3 and Prdm16, which are not related to MET-2, deposit the first methyl group at H3K9, allowing Suv39h enzymes to subsequently complete trimethylation. H3K9 modification thus regulates chromatin organization and expression in eukaryotic cells.

DNA Goes In One Door and Out the Other

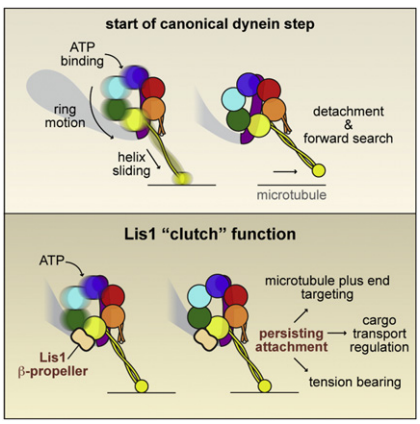
PAGE 961

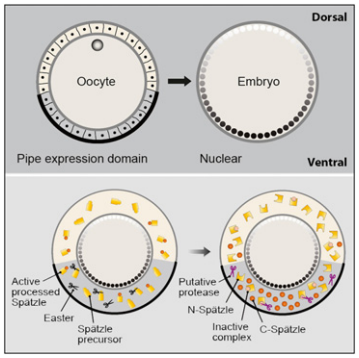
Sister-chromatid cohesion is mediated by entrapment of replicated DNAs inside a tripartite cohesin "ring" composed of Smc1, Smc3, and α-kleisin subunits. Chan et al. find that a "releasing" activity regulated by cohesin acetylation catalyzes DNA escape by opening its Smc3/α-kleisin interface. Because DNA entry involves the Smc1/Smc3 interface, the findings imply that cohesin has separate gates for DNA entry and exit.

Lis1 Engages Dynein for the Long Haul

PAGE 975

Lis1 is essential for intracellular transport and neuronal migration through its association with cytoplasmic dynein. Huang et al. show that Lis1 binds at the interface between dynein's ATPase- and microtubule-binding domains, where it operates like a molecular "clutch" that allows dynein to resist dissociating from microtubules. These data provide a molecular basis for dynein functions in living cells that require prolonged microtubule attachments.





Self-Governed Gradient Formation

PAGE 1016

Morphogen gradients pattern tissues and organs during development. One key question is how expression of a morphogen broadly within a domain can be sharpened into a functional gradient. Ittah et al. combine mathematical modeling and experimental validation to show that, in the fly embryo, processing the Spätzle ligand into active and inhibitor fragments that have opposite effects on the activity of Spätzle's receptor Toll drives formation of a sharp ventral gradient of Toll signaling. Dynamic localization of the inhibitor corrals the active ligand, shaping the region of Toll signaling.

HSP90 Seeks an Unstable Partner

PAGE 987

The Hsp90 chaperone promotes the folding and function of a diverse set of proteins, but the principles of substrate recognition by Hsp90 have remained elusive. Taipale et al. quantitatively survey interactions between human Hsp90 and the majority of kinases, E3 ligases, and transcription factors. Surprisingly, HSP90 does not bind particular sequence motifs but, rather, associates with intrinsically unstable kinases. In addition, the cochaperone CDC37 serves as a specific adaptor for recognizing kinases.

Precision Plane-ing in Stem Cell Divisions

PAGE 1002

Cruz-Ramirez et al. show that stem cells in the root meristem integrate both radial and longitudinal gradients of tissue patterning determinants to ensure that only specific stem cells undergo asymmetric cell divisions. A genetic regulatory circuit interprets information from these two developmental axes, and relying on bistability and protein degradation to reset cell states during division, it enables precise positioning of stem cell division planes despite noisy inputs.

Masquerader Muzzles a Cry for Help

PAGE 1029

By integrating structural, biochemical and functional analyses, Dong et al. show that the virulence effector proteins VirA from *Shigella flexneri* and EspG from *Enteropathogenic E. coli* (EPEC) inactivate the GTPase Rab1 via a catalytic mechanism that is similar to that employed by the host's GTPase-activating proteins (GAPs), although the effectors are structurally distinct from host GAPs. Through the action of these proteins, *Shigella* counteracts autophagy-mediated host defense, and EPEC muzzles the immune response by blocking host cytokine secretion.

Hey, Give Me Some of That!

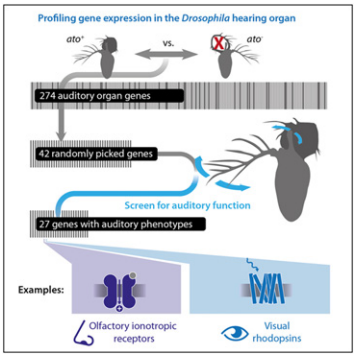
PAGE 1055

Long-term stress causes deficits in learning and memory. Liu et al. show in mice that these deficits are associated with an increase in the leakiness of RyR2 calcium channels of the endoplasmic reticulum and that targeting this channel with a small molecule alleviates impairment in learning and memory tasks.

Human Protein Complexes in Full

PAGE 1068

Analysis of the human protein interactome is crucial to expanding our understanding of basic protein relationships and molecular functions. Havugiman et al. couple extensive biochemical fractionation with quantitative mass spectrometry to characterize native multiprotein complexes from human cells. The authors generate a network enriched in stable protein assemblies, encompassing putative unannotated components of known complexes as well as novel complexes, many of which are broadly evolutionary conserved or linked to human disease.



Envisioning Hearing

PAGE 1042

Senthilan et al. identify nearly 300 new genes specific to the *Drosophila* auditory organ, roughly 80% of which have a mammalian homolog. Functional analyses in flies reveal that ion channels, motors, chemoreceptors, and virtually the entire phototransduction complex are important for hearing. The findings reveal new functions for ionotropic receptors and visual rhodopsins, demonstrating the common components shared by different sensory systems.